A practical guide to diagnosis, management and treatment of testosterone deficiency for Canadian physicians

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Abstract

The percentage of men receiving appropriate management for testosterone deficiency syndrome (TDS) is small in comparison to prevalence estimates. This is despite linkages to cardiovascular disease, osteoporosis, diabetes, sexual function, sarcopenia, emotional well-being and the metabolic syndrome. Furthermore, the availability of guidelines has not significantly enhanced the care of TDS patients. A multidisciplinary group of medical experts sought to improve the management of testosterone-deficient patients by Canadian physicians. This report describes their conclusions and defines an algorithm for appropriate TDS management.

Résumé

Le pourcentage d'hommes recevant une prise en charge appropriée pour un syndrome de carence en testostérone est faible en comparaison avec les taux de prévalence évalués, et ce, malgré le lien entre ce syndrome et les maladies cardiovasculaires, l'ostéoporose, le diabète, la fonction sexuelle, la sarcopénie, le bien-être émotionnel et le syndrome métabolique. Par ailleurs, la publication de guides de pratique n'a pas amélioré de façon significative les soins offerts aux patients atteints du syndrome de carence en testostérone. Une équipe multidisciplinaire de médecins a tenté d'améliorer la prise en charge des patients atteints de ce syndrome par les médecins canadiens. Le présent rapport décrit leurs conclusions et propose un algorithme de prise en charge.

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Introduction

Testosterone deficiency syndrome (TDS), formerly termed andropause, is characterized by a deficiency in serum testosterone (T) levels with or without changes in receptor sensitivity to androgens. This syndrome is also variably referred to as hypogonadism or late-onset hypogonadism (LOH). There are various clinical manifestations of TDS (Fig. 1).

Reduced T levels have been associated with the intake of certain medications (e.g., ketoconazole, spironolactone, estrogens, methadone) and the presence of comorbid conditions, such as diabetes, hypothyroidism, chronic obstructive pulmonary disease (COPD), obesity, hemochromatosis and the metabolic syndrome (MetS).[1,2] Testosterone levels also decline with age, and a subset of men over age 40 may display clinically relevant TDS.[3,4] It is expected that over the next 40 years life expectancy in North America will increase by 4.8 years.[5] Therefore, it is likely that the prevalence of TDS will rise during this period from the current Canadian crude prevalence rates that show 25% of men aged 40 to 62 years as biochemically testosterone deficient.[6]

Recent consensus recommendations and guidelines for TDS diagnosis and management are available;[1,4] yet, less than 10% of affected individuals receive T therapy,[7] suggesting underutilization of these guidelines. Barriers to proper diagnosis and management may include: (1) a lack of physician awareness on associated diseases (such as MetS, diabetes and cardiovascular disease) and the ability of testosterone replacement therapy (TRT) to reduce disease symptoms,[8-11] (2) unfounded concerns about prostate health[4,12] and (3) insufficient dissemination of the guidelines in Canada. To reduce these barriers a multidisciplinary panel convened with the goal of improving TDS knowledge transfer to Canadian physicians. (A panel of urologists, endocrinologists and family physicians met in Toronto, February 5 to 6, 2010. The relevant literature was reviewed and consensus recommendations were formulated.) This report summarizes the essential findings of the panel into key recommendations and a concise, practical TDS management algorithm (Fig. 2).

Detection and selective screening for TDS

Effective management of TDS begins with an initial screening of high-risk men. A proportion of males with certain clinical disorders exhibit a high prevalence of low T levels (Table 1).[1] The incidence of diabetes and T deficiency are directly correlated: 33% of men with diabetes have hypogonadism,[13] and men with higher levels of T (15.6–21.0 nmol/L) have a 42% lower risk of type II diabetes.[14] In particular, the Canadian Diabetes Association guidelines state that all men with diabetes should be screened for erectile dysfunction (ED), as 34% to 45% of men with diabetes have

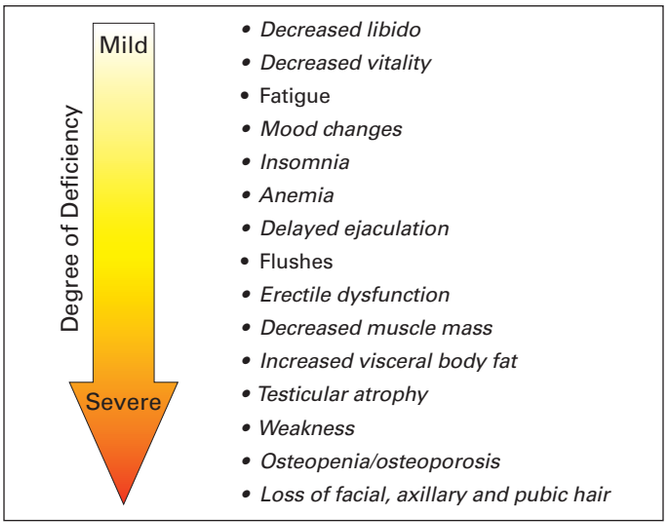

Fig. 1. Clinical manifestations of testerone deficiency.

ED.[15] The Endocrine Society guidelines also suggest that all men with Type II diabetes be screened for testosterone deficiency.[1]

Alternatively, patients may report symptoms consistent with TDS, such as fatigue, insomnia, decreased libido, reduced vitality, mood changes and ED.[1,4] A thorough history and physical examination may reveal other clinical manifestations that are often consistent with the degree of T deficiency (Fig. 1).[1,4,16,17] These manifestations may be present alone or in combination.

Screening questionnaires have been developed to record and evaluate patient history and symptoms. The Androgen Deficiency in Aging Males (ADAM) instrument (Appendix 1) is most widely accepted. This questionnaire has been evaluated for its correlation with serum levels of T;[6,18] although it shows high sensitivity (88%[6] and 81%[18]), its specificity is marginal (66%[6] and 21.6%[18]). Good sensitivity indicates that the ADAM questionnaire correctly identifies those individuals with biochemically low T, but a lack of specificity may lead to inappropriate classification of men as hypogonadal or normal.

Diagnosis of TDS

Patients with symptoms suggestive of TDS require biochemical evaluation of serum T. Circadian rhythm influences T levels: higher T values are obtained in the morning.[19] As a result, blood samples should be obtained between 7 and 11 am.[4]

Serum T circulates in a free or bound state. Most T is bound to either sex hormone-binding globulin (SHBG) (60%) or albumin (38%). Testosterone is tightly bound to SHBG, but weakly bound to albumin. Consequently, both albumin-bound T and free T (FT) are accessible to target tissues and constitute the bioavailable (BT) fraction that carries out the actions of T. Sex hormone-binding globulin-bound T is not biologically active. Generally, TDS manifestations correlate with the degree of T deficiency.[16]

The panel recognized measured BT as the gold standard for biochemistry. Additionally, the ammonium sulphate precipitation technique correlates well with symptoms of TDS.[20] If measured BT is unavailable or unaffordable, calculated free T (cFT), calculated bioavailable T (cBT) or total T (TT) are acceptable alternatives.[21] A free calculator for cFT and cBT is available online at the website for the International Society for the Study of the Aging Male (www.issam.ch). The calculated methods closely correlate with FT values obtained through laboratory assays, yet there are shortcomings: (1) SHBG levels vary up to twofold with different assays, and (2) aging and illness alter the binding characteristics of SHBG or serum.

The panel has not defined cut-off values for normal T levels because of difficulties with equipment standardization and interlaboratory variability. Instead, it is recommended that physicians consistently use the same local laboratories and gain familiarity with the accuracy, precision and definition of normal values for the assays offered in their community.

Some men may show marked intraindividual weekly variability in T values,[22] and up to 50% of young healthy men have temporary T levels below the normal range in a 24-hour period.[23] Therefore, abnormal (low or borderline) T levels require confirmation with a repeat T determination plus SHBG and a measure of serum luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin. In young men, chronic elevation of LH and FSH, combined with low levels of T, is clearly diagnostic of primary (testicular) hypogonadism. These diagnostic criteria are not as clearly defined in older men. Patients with secondary hypogonadism (hypothalamic-pituitary) have low T and normal LH and FSH levels. A combination of primary and secondary causes of TDS is often at play.

Table 1. Clinical disorders or conditions associated with a high prevalence of low T levels

Type II diabetes mellitus
Metabolic syndrome
Human immunodeficiency virus-associated weight loss
Treatment with opioids, glucocorticoids or ketoconazole
Osteoporosis or low trauma fracture at a young age
End-stage renal disease and maintenance hemodialysis
Chronic obstructive pulmonary disease
Infertility
Sellar region mass, disease, radiation or trauma
Use of street drugs
Liver disease

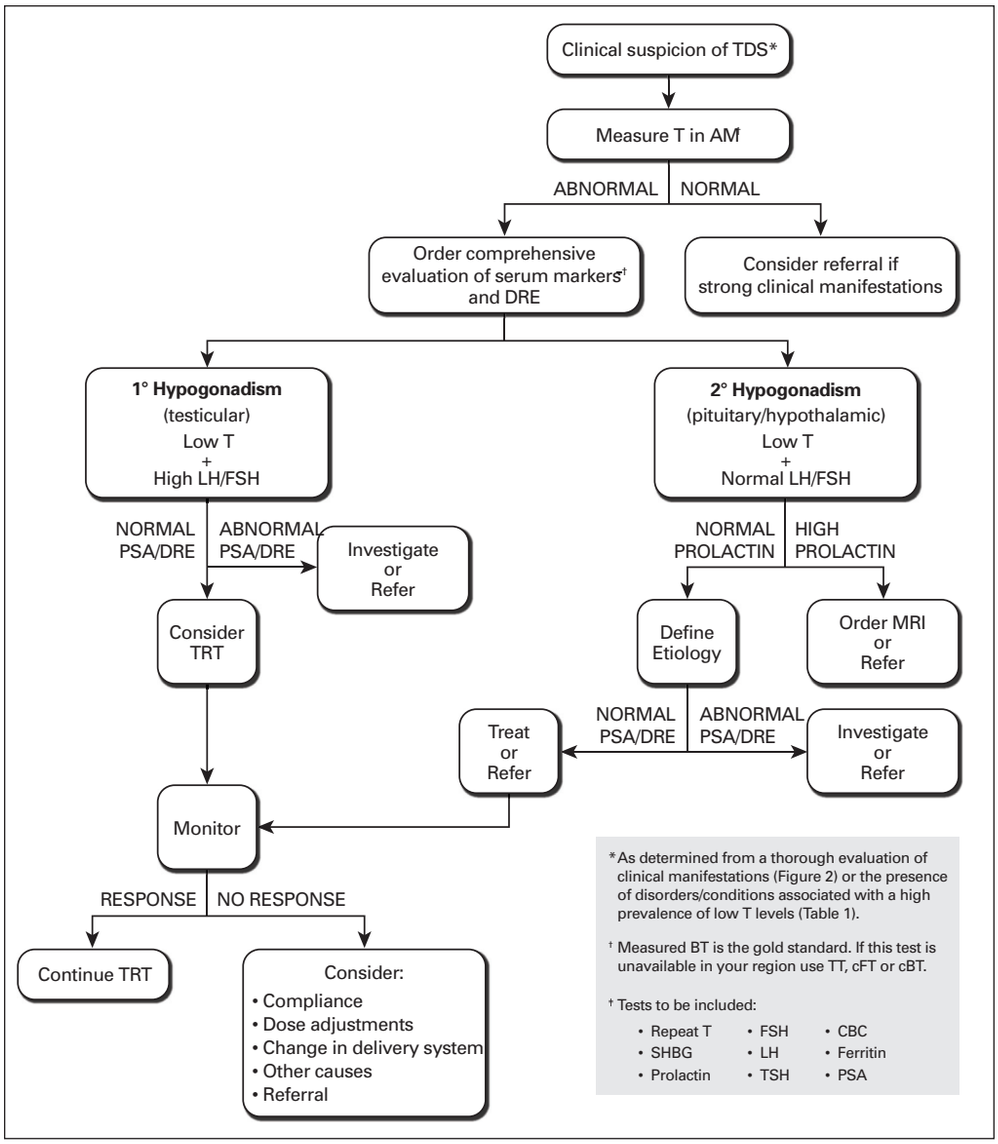

Fig. 2. A practical management algorithm for TDS.

For definitive diagnosis of hypogonadism, physicians should rule out other clinical conditions that may masquerade as TDS. For example, some symptoms of TDS are consistent with depression or hypothyroidism, the latter diagnosed through detection of elevated serum thyroid-stimulating hormone (TSH). Measures of prolactin and ferritin can exclude hyperprolactinemia and hemochromatosis, respectively. Physicians should consider referral in patients with elevated prolactin levels. To exclude the possibility of pituitary/hypothalamic lesions, magnetic resonance imaging (MRI) should be performed in patients with very low levels of T and persistent hyperprolactinemia,[24,25] or in patients with prolactin levels greater than 2 times the upper normal limit.[26]

Treatment of TDS

Testosterone formulations

Testosterone replacement therapy is suggested in patients with TDS. The goal of treatment is symptom improvement and achievement of physiological T levels. A number of safe and effective T products have been developed for treatment with varying delivery mechanisms. The currently available approved formulations in Canada include injectable, oral and transdermal agents (Table 2).

Intramuscular injection products include testosterone cypionate (Depo-Testosterone[27]) and testosterone enanthate (Delatestryl[28]). These preparations are relatively inexpensive, effective and long-acting.[29] Both products induce supraphysiologic serum T levels in the first few days of the cycle. These formulations also have a waning effect that can result in the reappearance of T deficiency manifestations towards the end of the treatment cycle (2 to 3 weeks after injection).

Testosterone undecanoate is formulated in Canada in the convenience of an oral preparation (Andriol[30] or pms-Testosterone[31]). These products may induce supraphysiologic levels of dihydrotestosterone.[32] To permit absorption, testosterone undecanoate must be taken with a high-fat meal. Absorption issues may lead to poor responses.

Two transdermal T products are also available in Canada. Testosterone gels (AndroGel[33] and Testim[34]) are transdermal gels applied daily to the skin that achieve consistent T levels.[35-37] Side effects of the gels are minimal, mainly minor skin reactions. Patients may prevent secondary exposure through contact transfer by washing their hands after applying the gel, covering the application sites with clothing, and washing the site thoroughly prior to anticipated skin-to-skin contact with another individual.

Table 2. Common testosterone formulations available in Canada

Generic name	Trade name	Dosage
Injectables		
Testosterone cypionate	Depo-testosterone	200-400 mg every 2 weeks
Testosterone enanthate	Delatestryl	100-400 mg every 1-4 weeks
Oral Medication		
Testosterone undecanoate	Andriol pms-Testosterone	Initial dose of 120-160 mg per day in 2 divided doses
Transdermals		
Testosterone patch	Androderm	2.5 or 5 mg per day
Testosterone gels	AndroGel Testim	5-10 g of gel per day

The transdermal patch (Androderm[38]) is an alternative to the gels with similar effectiveness; however, visibility and significant skin reactions are drawbacks of this product.[39,40]

The choice of T formulation should be based on physician and patient discussions with regard to the ASTEP acronym: availability, safety, tolerability, efficacy and preference. Physicians should be aware of the suggested follow-up periods and adverse events of each T product.

Benefits of TRT

Testosterone treatment has been shown to improve many of the symptoms of TDS and enhance overall health and potentially survival.[41] Clinical studies indicate that T therapy enhances strength,[42] sexual desire,[43,44] energy,[45] emotional well-being and cognition.[45-47] Bone mineral density (BMD) is increased by T therapy in men with low T levels.[48,49] Testosterone replacement therapy reduces body fat,[50] enhances glycemic control in diabetic patients and may improve some components of MetS.[8] Men with profound hypogonadism show significant improvement in ED when on TRT.[35,51] Evidence is emerging that T may also improve cardiovascular health in hypogonadal men.[9-11]

Contraindications to TRT

Patients should be evaluated for other medical conditions that may lead to adverse events upon treatment. Testosterone therapy is absolutely contraindicated in men with breast or prostate carcinomas.[1,4] Prior to initiation of T therapy, it is recommended that physicians measure the prostate-specific antigen (PSA) level and perform a digital rectal examination (DRE). Patients with abnormal PSA or DRE findings should be referred to a urologist for further evaluation.

Testosterone therapy may also worsen other medical conditions, including erythrocytosis, untreated obstructive sleep apnea and severe congestive heart failure.[50,52]

Table 3. Common alternative/complementary approaches to testosterone replacement therapy for the management of testosterone deficiency syndrome manifestations

Approach	Anticipated outcomes
Diet and exercise	Healthy weight reduction Improved muscle strength Enhanced emotional well-being
Bisphosphonates	Increased bone mineral density
Antidepressants	Enhanced emotional well-being
Continuous positive airway pressure	Treatment of sleep apnea
Phosphodiesterase-5 inhibitors	Improved erectile function
Discontinuation of opioids	Improvement in multiple symptoms of hypogonadism

Erythrocytosis can be revealed through a complete blood count (CBC). Testosterone replacement therapy is not suggested for men wishing biological fatherhood as T may reduce sperm production. Treatment with T in men with any of these medical conditions should not be initiated until these issues have been addressed

Alternative treatments to TRT

Occasionally, some testosterone deficiency manifestations can be managed with reversal of an underlying cause, drug therapy or lifestyle modifications (Table 3). Treatment of sleep apnea,[53] weight reduction[54] and discontinuation of opioid medication[55] may improve manifestations of T deficiency. Yet, the poor adherence to many of these regimens (e.g., diet and exercise) makes T therapy a logical option.

Monitoring

Patients should be examined regularly for symptom response and changes in blood parameters. Monitoring should occur every 3 to 6 months in the first year and at yearly intervals thereafter if the patient is stable. Some improvements in the clinical manifestations of TDS may be observed in the first 3 to 6 months of TRT, while other symptoms may take longer to resolve (Fig. 3).[4] Non-response may be indicative of compliance issues, malabsorption, insufficient dose, an unsatisfactory formulation or symptoms unrelated to TDS. Long-term lack of response may require referral to a specialist. Combination therapy with T and phosphodiesterase-5 inhibitors (PDE5i) may prove useful in ED patients who fail initial treatment with T alone. Likewise, ED patients who fail initial therapy with PDE5i alone should be screened for T deficiency and may benefit from the addition of T to their treatment regimen.

At each appointment, the patient should undergo an assessment of clinical response and adverse events. Levels of serum T and hemoglobin should be determined along with a hematocrit. Prostate health should be assessed by

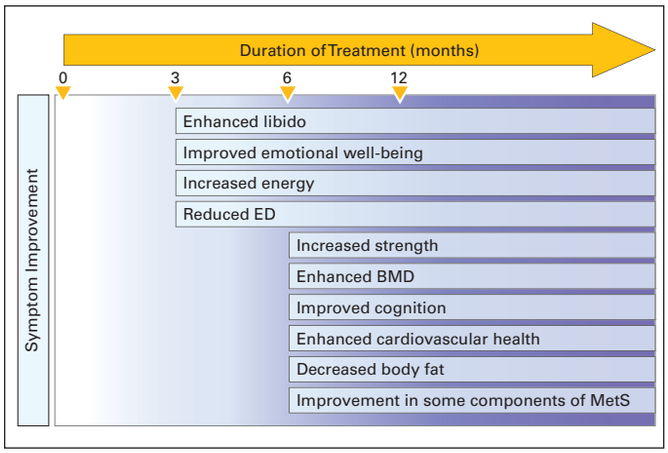

Fig. 3. Anticipated symptom improvement of TRT and approximate timeliness of visualization.

PSA and DRE. The patient should be referred if DRE findings are suspicious or PSA levels increase. An elevated hematocrit is characteristic of erythrocytosis, which can develop from T treatment (particularly the depot formulations). These patients should receive dose adjustments or a change of delivery form to maintain hematological values within a normal range.[1,35]

Conclusions

This paper highlights several key features of TDS:

- The prevalence of TDS is significant in men over 40 years of age, but only a small proportion is treated adequately.
- Testosterone deficiency syndrome is a significant health issue because of the association of low T levels with diabetes, cardiovascular disease, osteoporosis and a decrease in life quality and expectancy.
- Diagnosis of TDS requires the presence of clinical manifestations and laboratory confirmation of abnormal T levels.
- Confirmed TDS may be managed with lifestyle modifications and appropriate use of an injectable, oral or transdermal T preparation.
- Symptom response and safety of TRT should be monitored regularly with a physical examination, comprehensive serum analysis and DRE.

Appendix A.
ADAM Questionnaire*
A positive answer represents Yes to questions 1 or 7 or any 3 other questions

YES	NO	
☐	☐	1. Do you have a decrease in libido (sex drive)?
☐	☐	2. Do you have a lack of energy?
☐	☐	3. Do you have a decrease in strength and/or endurance?
☐	☐	4. Have you lost height?
☐	☐	5. Have you noticed a decreased enjoyment of life?
☐	☐	6. Are you sad and/or grumpy?
☐	☐	7. Are your erections less strong?
☐	☐	8. Have you noticed a recent deterioration in your ability to play sports?
☐	☐	9. Are you falling asleep after dinner?
☐	☐	10. Has there been a recent deterioration in your work performance?

* Morley et al. (6).

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